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Clinical impact and risk factors for colonization with extended-spectrum β-lactamase-producing bacteria in the intensive care unit

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Abstract *Purpose:* The changed epidemiology of extended spectrum beta-lactamases (ESBL), the spread to the community and the need for prudent use of carbapenems require updated knowledge of risk factors for colonization with ESBL-producing enterobacteriaceae (ESBL-PE). *Methods:* An 8-month prospective study in the medical ICU of an 850-bed general and university-affiliated hospital. *Results:* Of 610 patients admitted, 531 (87 %) had a rectal swab obtained at admission, showing a 15 % (82 patients) ESBL-PE carriage rate, mostly of *E. coli* ($n = 51$, 62 %); ESBL-PE caused 9 (3 %) infections on admission. By multivariable analysis, transfer from another ICU (OR = 2.56 [1, 22]), hospital admission in another country [OR = 5.28 (1.56–17.8)], surgery within the past year [OR = 2.28 (1.34–3.86)], prior neurologic disease [OR = 2.09 (1.1–4.0)], and prior administration of third generation cephalosporin (within 3–12 months before ICU admission) [OR = 3.05 (1.21–7.68)] were independent predictive factors of colonization by ESBL-PE upon ICU admission. Twenty-eight patients (13 % of those staying for more than 5 days) acquired ESBL carriage in ICU, mostly with *E. cloacae* ($n = 13$, 46 %) and *K. pneumoniae* ($n = 10$, 36 %). In carriers, ESBL-PE caused 10 and 27 % of first and second episodes of ICU-acquired infections, respectively. *Conclusion:* We found a high prevalence of ESBLE-PE colonization on admission to our ICU, even in the subgroup admitted from the community, but few first infections. Identifying risk factors for ESBL-PE colonization may help identifying which patients may warrant empiric ESBL-targeted antimicrobial drug therapy as a means to limit carbapenem use.

Keywords Antimicrobial agents · Community-acquired infection · Non-pulmonary nosocomial infections

Introduction

In gram-negative pathogens, beta-lactamase production remains the most important contributing factor to antimicrobial resistance. Cases of infections with extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBL-PE) were first reported during the late 1980s and have subsequently spread worldwide [1–3]. The emergence of CTX-M-type ESBLs has modified the epidemiology of ESBLs since dissemination of these enzymes is not restricted to the healthcare setting but also involves the community, especially among *Escherichia coli* [4–10]. Since the beginning of the century, the prevalence of infection with ESBL, notably among *E.coli* and *Klebsiella pneumoniae*, has increased dramatically [11–13]. Infections caused by ESBL producers have been associated with severe adverse clinical outcomes, leading to increased mortality, prolonged hospital stay, and increased costs [14–17], mostly because of delayed effective therapy. Consequently, carbapenems are increasingly used by intensivists as empiric therapy of hospital-acquired sepsis. This vicious circle of bacterial resistance already leads to a rapid worrying international dissemination of carbapenemase-producing enterobacteriaceae (CPE), especially among *K. pneumoniae* (KPC) [18–20]. New agents against these multi-drug-resistant bacteria are not going to be available soon, and the intensivist's armamentarium is close to a dead end without the cautious use of carbapenems [21]. An important risk factor for nosocomial infection is prior colonization [22]. The changed epidemiology, the spread of ESBL to the community, and the need for prudent use of carbapenems require updated studies to identify current risk factors for colonization with ESBL-PE.

The primary objective of our study was to determine which factors are predictive of colonization with ESBL-PE at admission to an intensive care unit (ICU). The secondary objectives were to identify the rates of and risk factors for acquisition of ESBL-PE during the ICU stay. We also examined the occurrence and risk factors of ESBL-PE infections in relation to carriage of ESBL-PE.

Patients and methods

Setting and patients

This 8-month prospective study (1 October 2010–31 May 2011) was conducted in the medical intensive care unit of a French 850-bed general and university-affiliated hospital. The ICU includes 13 beds with 5 single rooms, and a step-down unit of 11 beds with 3 single rooms. No specific isolation precautions were being used during the study for patients with ESBL-producing bacteria recovered from clinical or screening cultures, and contact isolation precautions were applied only for patients with carbapenemase-producing organisms, *Clostridium difficile*, methicillin-resistant *S. aureus*, and vancomycin-resistant enterococci. However, an active hand hygiene improvement program with repeated auditing and feedback, as well as twice weekly surveillance of patients for ESBL-producing bacteria using rectal swabs, had been conducted for 2 years as part of 'MOSAR,' an ongoing EC-funded (FP-6) study. In addition, daily body washings with chlorhexidine were routinely used for all patients. This study was approved by our Institutional Review Board (CPP Ile de France IX), and informed consent was waived.

Rectal swabs were collected from each patient within 24 h of ICU admission and twice weekly for the duration of hospitalization in the ICU. We excluded readmissions. ESBL-PE acquisition was defined as a positive rectal swab culture after a negative admission swab. Rectal swab samples were screened for ESBL-PE on chromogenic agar (Oxoid Ltd, Cambridge, UK), and ESBL production was confirmed by the double-disk diffusion method using ceftazidime or cefotaxime with clavulanic acid [23] (see the ESM for details).

Demographic, clinical, and laboratory data

A detailed clinical profile of each patient was established from the patient's medical record, referral documents (e.g., from the family physician or nursing home), interviews with each patient and/or his or her family, and previous hospital admission records. The following data were collected: demographic characteristics, the simplified acute physiology score (SAPS II), days and in hospital location before ICU admission when appropriate, main reason for admission, hospital admission and administration of antibiotics in the previous year (stratified according to within 3 months of admission or earlier), prior antibiotic exposure (class and duration), surgery in the previous year, presence of underlying diseases and Charlson comorbidity index [24], and whether any indwelling tubes were in place for more than 24 h before ICU admission.

We defined colonization pressure as the sum of the daily proportion of patients in the unit colonized with ESBL-PE during the days preceding acquisition or ICU discharge [25].

The clinical impact of ESBL-PE colonization in the ICU was assessed from the rate of positive clinical samples until hospital discharge, mortality rate and length of stay, and comparing ESBL-PE carriers with non-carriers, and the primary outcome was defined as the rate of infection with ESBL-PE, contrasting early and late infection in carriers and non-carriers.

Statistical analysis

Results are reported as medians and interquartile ranges (25th–75th percentiles) or numbers with percentages.

Associations between each variable and colonization with ESBL-PE at ICU admission were tested using the χ^2 or Fisher's exact test for categorical data and by the Mann-Whitney *U* test for continuous data. We used multivariable logistic regression with a backward procedure to identify patients' characteristics associated with ESBL-PE colonization at ICU admission. Variables selected by bivariate analysis ($P < 0.10$) and those considered clinically relevant were entered in a logistic regression model. Considering the number of events, a maximum of eight variables was entered in a two-step model, first including baseline characteristics, then antibiotic exposures [26]. Results are expressed as crude and adjusted odds ratios (OR) with their 95 % confidence intervals (CI). A *P* value <0.05 was considered statistically significant. A similar analysis was conducted for the subgroup of patients admitted from the community, defined as those admitted directly from home or having stayed in the hospital for <48 h before ICU admission.

To examine risk factors for ESBL acquisition, we selected patients without ESBL colonization at admission, staying 5 days or more in the ICU and having at least two screening samples obtained before ICU discharge. Additional analyses were performed to identify risk factors for subsequent culture positivity with ESBL-PE among all the patients and among the subgroup of patients colonized with ESBL-PE. Statistical analyses used the Stata software, version 10.1 (StataCorp, College Station, TX, USA).

Results

ESBL-PE colonization at ICU admission

During the study period, 610 patients had at least one ICU admission, of which 531 (87 %) had a screening sample obtained within 24 h of ICU admission. The remaining 79 patients had similar characteristics (data not shown) but a much shorter length of ICU stay (2 days [2, 3] vs. 5 days [3–10]) and were not screened for ESBL carriage.

The median age of the 531 patients was 64 years (50–75); 198 (37 %) had a Charlson comorbidity index of > 2. Within the previous year, 231 (43 %) patients had been hospitalized for more than 24 h and 242 (46 %) had been exposed to antibiotics.

Eighty-two (15 %) patients were detected to be ESBL-PE carriers on the admission screening sample, mostly of *E. coli* ($n = 51$; 62 %) or *K. pneumoniae* ($n = 15$; 18 %). Table 1 shows the main characteristics of the patients and those associated with colonization at ICU admission. By multivariable analysis (Table 2), transfer from another ICU, previous hospital admission in another country, surgery within the past year, prior neurologic disease, and prior administration of third generation cephalosporin (within 3–12 months before ICU admission) remained associated with colonization by ESBL-PE upon ICU admission; exposure to fluoroquinolones within the past 3 months fell short of statistical significance ($P = 0.062$). The final model showed a good calibration (Hoshmer-Lemeshow $\chi^2 = 2.13$; $P = 0.54$), but limited discrimination (area under the curve, 0.68).

In the subgroup of 394 (74 %) patients admitted from the community, 49 (12 %) were found colonized by an ESBL-PE on the admission screening sample, 41 (84 %) of which were *E. coli.* Independent predictive factors of colonization by ESBL-PE at ICU admission in this subgroup included a previous hospital admission within 3–12 months before admission, prior urinary tract disease, and exposure to third generation cephalosporin (Table 2); again treatment with fluoroquinolone within the past 3 months fell short of statistical significance ($P = 0.077$). The final model again showed good calibration ($\chi^2 = 0.19$; $P = 0.91$) but limited discrimination (area under the curve, 0.69).

ESBL-PE-acquired carriage in ICU

At least two screening samples were obtained in 212 patients without detectable colonization with ESBL-PE on admission and staying at least 5 days in the ICU. Twenty-eight (13 %) acquired ESBL carriage, detected a median of 9 days [8–20] after ICU admission. Thirteen (46 %) were *Enterobacter cloacae*, ten (36 %) were *K. pneumoniae*, and only two (7 %) were *E. coli* (see the ESM Table). Two patients (7 %) had several ESBL-PE species identified (*K. pneumoniae* with *E. coli* or *C. diversus*). No carbapenemase-producing enterobacteriaceae was detected. Factors associated with ESBL acquisition in the ICU found by univariate and multivariable analyses are shown in Tables 3 and 4, respectively. Prior exposure to third generation cephalosporins or to a β-lactam + inhibitor (within 3 months of ICU admission) were both strongly associated with ESBL-PE acquisition. The final model showed both a good calibration ($\chi^2 = 2.32$; $P = 0.97$) and discrimination (area under the curve, 0.89).

Impact of ESBL-PE on infections in the ICU

During the 8-month study period, 210 patients had community-acquired infection on admission (Fig. 1). Only three such patients (1.4 %, or 6.1 % of ESBL-PE carriers) were infected with ESBL-PE on admission (all urinary tract infection), one of whom received a delayed effective therapy. Of 84 patients with hospital-acquired infections identified at ICU admission, 6 (7.1 %) were caused by ESBL-PE, including pulmonary infection ($n = 3$), and urinary tract infection, catheter-related bloodstream

Table 1 Univariate analyses of variables associated ESBL colonization at ICU admission in 531 patients screened

Variables	ESBL− ($n = 449$)	ESBL+ ($n = 82$)	OR (95 % CI)	P value
Male gender	274 (61 %)	46 (56 %)		0.40
Age, median [IQR]	64 [50–75]	64 [49–76]		0.66
Age >75 years	113 (25 %)	22 (27 %)		0.75
Medical admission	399 (89 %)	75 (91 %)		0.48
Main reason for ICU admission				
Acute respiratory failure	206 (46 %)	31 (38 %)		0.18
Metabolic/AKI	21 (5 %)	3 (4 %)		1
Neurologic disorder/coma	45 (10)	9 (11 %)		0.76
Cardiac arrest	33 (7 %)	1 (1 %)	0.16 (0.2–1.17)	0.04
Drug intoxication	27 (6 %)	2 (2 %)		0.3
Severe sepsis/septic shock	73 (16 %)	24 (29 %)	2.1 (1.2–3.6)	0.005
Hemorrhagic shock	13 (3 %)	4 (5 %)		0.31
Other shock	17 (4 %)	1 (1 %)		0.33
Diffuse dermatitis	5 (1 %)	3 (4 %)		0.1
Others	10 (2 %)	3 (4 %)		0.43
SAPS II, median [IQR]	34 [23–49]	35 [25–46]		0.70
Admission during previous year	185 (41 %)	50 (61 %)	2.2 (1.4–3.6)	0.001
Hosp. <3 months	125 (28 %)	33 (40 %)	1.7 (1.1–2.8)	0.024
3 months <Hosp <1 year	121 (27 %)	38 (46 %)	2.3 (1.4–3.8)	<0.001
Both <3 months and >3 months	61 (14 %)	21 (26 %)	2.2 (1.2–3.9)	0.006
In another country	6 (1 %)	7 (9 %)	6.9 (2.25–21.0)	0.001
Location before ICU admission				
Hospital days before ICU	0 [0–2]	1 [0–10]		0.001
Another ICU	30 (7 %)	18 (22 %)	3.9 (2.1–7.5)	<0.001
Emergency/home	280 (62 %)	38 (46 %)	0.5 (0.32–0.84)	0.006
Nursing home	9 (2 %)	1 (1 %)		1
Other	130 (29 %)	25 (30 %)		0.78
Urinary catheter >24 h	42 (9 %)	20 (24 %)	3.2 (1.75–5.78)	<0.001
Venous catheter >24 h	36 (8 %)	18 (22 %)	3.3 (1.76–6.14)	<0.001
Mechanical ventilation >24 h	12 (3 %)	6 (7 %)	2.9 (1.06–8.02)	0.042
Comorbidities				
Charlson comorbidity index	2 [0–3]	3 [1–4]		0.003
Charlson >2	156 (37 %)	42 (52 %)	2.0 (1.26–3.27)	0.003
Chronic pulmonary disease	84 (19 %)	13 (16 %)		0.54
Diabetes mellitus	121 (27 %)	22 (27 %)		0.98
Neurologic disease	51 (11 %)	17 (21 %)	2.0 (1.1–3.7)	0.02
Immunodeficiency	113 (25 %)	29 (35 %)		0.055
Liver cirrhosis	30 (7 %)	9 (11 %)		0.17
Chronic renal insufficiency	45 (10 %)	13 (16 %)		0.12
Dialysis	13 (3 %)	2 (2 %)		1
Congestive heart failure	124 (28 %)	31 (38 %)		0.062
Urinary tract disease	8 (2 %)	6 (7 %)	4.4 (1.49–13.1)	0.011
Prior surgery				
Surgery <1 year	69 (15 %)	26 (32 %)	2.6 (1.5–4.3)	<0.001
3 months <Surgery <1 year	31 (7 %)	14 (17 %)	2.8 (1.4–5.4)	0.002
Surgery <3 months	42 (9 %)	15 (18 %)	2.2 (1.14–4.1)	0.016
Prior antibiotics				
Antibiotic therapy <1 year	190 (42 %)	52 (63 %)	2.45 (1.5–4.01)	<0.001
Ab <1 year and broad-sp.	161 (36 %)	46 (56 %)	2.36 (1.46–3.81)	<0.001
Ab <3 months	150 (33 %)	44 (54 %)	2.38 (1.47–3.84)	<0.001
Ab <3 months and broad-sp.	126 (28 %)	40 (49 %)	2.47 (1.53–4.01)	<0.001
Ab <3 months and >10 days, broad-sp.	76 (17 %)	34 (42 %)	3.5 (2.13–5.85)	<0.001
Aminopenicillins	29 (6 %)	10 (12 %)		0.059
Penicillin +iBL	66 (15 %)	22 (27 %)	2.17 (1.25–3.8)	0.005
Fluoroquinolones	38 (8 %)	17 (21 %)	2.9 (1.54–5.44)	0.001
3GC	39 (9 %)	17 (21 %)	2.81 (1.5–5.27)	0.001
Carbapenem	8 (2 %)	8 (10 %)	6.05 (2.2–16.6)	<0.001
3 months <Ab <1 year	81 (18 %)	25 (31 %)	2.03 (1.2–3.45)	0.008
3 months <Ab <1 year and broad-sp.	67 (15 %)	21 (26 %)	2.01 (1.15–3.54)	0.013
Aminopenicillins	9 (2 %)	4 (5 %)		0.11
Penicillin +iBL	33 (7 %)	7 (9 %)		0.68
Fluoroquinolones	12 (3 %)	7 (9 %)	2.45 (1.31–9.06)	0.016
3GC	15 (4 %)	8 (10 %)	3.18 (1.3–7.76)	0.015
Carbapenem	2 (0.5 %)	1 (1 %)		0.39

Table 1 continued

Variables	ESBL− ($n = 449$)	ESBL+ ($n = 82$)	OR (95 % CI)	P value
Outcomes				
Duration of MV	4 [2–11]	5 [2–8]		0.66
Alive	363 (81 %)	70 (85 %)		0.22
ICU stay	5 [3–10]	7 [3.5–11]		0.051

Ab antibiotic, *AKI* acute kidney injury, *broad-sp.* broad-spectrum, *3GC* third generation cephalosporin, *hosp.* hospital, *iBL* beta-lactamase inhibitor, *[IQR]* interquartile range, *MV* mechanical ventilation

Table 2 Adjusted odds ratio (aOR) for ESBL-PE colonization at ICU admission in 531 patients, irrespective of their prior location (All), and in the subgroup of 394 patients admitted from the community

Patients	All ($n = 531$)	Admitted from the community ($n = 394$)
Variable	aOR [95 % CI]	
Surgery within past year	2.28 [1.34–3.86]	–
Hospital admission in another country	5.28 [1.56–17.8]	–
3 months <hospital admission <1 year	–	2.83 [1.46–5.45]
Prior neurologic disease	2.09 [1.10–4.00]	–
Transfer from another ICU	2.56 [1.26–5.22]	–
Prior urinary tract disease	–	6.03 [1.44–25.1]
Fluoroquinolones <3 months	1.95 [0.96–3.95]*	2.59 [0.90–7.45]**
3GC >3 months	3.05 [1.21–7.68]	3.58 [1.18–10.8]

* $P = 0.062$, ** $P = 0.077$

infection or septic arthritis (one each); one received delayed effective therapy. Among the 365 patients staying in the ICU for more than 3 days, we found 108 ICU-acquired infections in 87 patients (Fig. 2). Seven (6.5 %) of these were caused by ESBL-PE, including urinary tract infection ($n = 5$), or pulmonary infection and intra-abdominal infection with bacteraemia (1 each). None of these patients received delayed effective therapy. All patients with ICU-acquired infection caused by ESBL-PE also had rectal carriage, including 14 (82 %) with the same species; only one patient had infection before detection of carriage.

The median length of stay before the occurrence of ICU-acquired infections caused by ESBL-PE was 10 days [6–11]. Among the 90 patients staying in the ICU for more than 3 days and having ESBL-PE carriage either on admission or acquired during the ICU stay, ESBL-PE caused 4/41 (10 %) of first episodes and 3/11 (27 %) of the second episodes of ICU-acquired infection (Fig. 2). Eight further patients having clinical samples growing ESBL-PE were considered to have colonizations, which were not treated with antibiotics.

The median time elapsed between the detection of ESBL carriage in rectal swabs and detection of ICU-acquired infection was 5 days [3–9]. The few ESBL infections did not allow multivariate analysis of variables associated with infection caused by ESBL-PE.

The overall in-ICU mortality rate was 18 %, and the median length of stay was 5 days [3–10]. The mortality rate of the 110 ESBL-colonized patients and of the 16 patients having ESBL-PE infection was similar (19 %), as was their length of ICU stay (9 days [4–19] and 9 days [7–15], respectively).

Discussion

The main finding from this 8-month study of 531 patients is the high rate of rectal carriage of ESBL-PE on ICU admission (15 % overall and 12 % in patients admitted from the community), with *E. coli* representing the most common ESBL-PE species recovered (62 %). Second, infections caused by ESBL-PE were rarely (3 %, Fig. 1) observed on ICU admission despite this high carriage rate; conversely, such infection was more common (10 %) among patients with ICU-acquired infections, especially during second episodes (14 %, Fig. 2). This study is, to our knowledge, the first to analyze risk factors for ESBL-PE carriage at ICU admission and acquisition, based on prospectively collected and comprehensive information on patients' characteristics and exposures to antibiotics and other risk factors prior to and during ICU admission.

Most studies conducted in the past decade report an increasing incidence of ESBL-PE isolates recovered from both clinical and surveillance samples. Recent studies of colonization rates in ICU patients are sparse [27–30], with rates varying from 2 % [28] to as high as 49 % [30]. Although ESBL rates reported differ according to the regional area and patient populations studied, the overall

Table 3 Univariate analyses of variables associated with ESBL acquisition during ICU stay in 212 patients staying for 5 days or more and non-colonized on ICU admission

Variables	No acquisition ($n = 184$)	ESBL acquisition ($n = 28$)	Odds ratio (95 % CI)	*P* value
Male gender	109 (59 %)	24 (87 %)	4.1 (1.4–12.4)	0.007
Age >75 years	37 (20 %)	13 (46 %)	3.4 (1.5–7.9)	0.004
Medical admission	155 (84 %)	24 (86 %)		0.84
Main reason for ICU admission				
Acute respiratory failure	95 (52 %)	11 (39 %)		0.22
Neurologic disorder/coma	18 (10 %)	3 (10 %)		0.75
Cardiac arrest	11 (6 %)	1 (4 %)		0.68
Severe sepsis/septic shock	31 (17 %)	10 (36 %)	2.7 (1.1–6.5)	0.019
Other shock	13 (4 %)	2 (4 %)		0.57
Others	16 (6 %)	1 (0 %)		0.35
SAPS II, median [IQR]	36 [27–49]	48 [37–56]		0.004
Comorbidities				
Charlson >2	66 (36 %)	14 (50 %)		0.15
2-bedded room	150 (81 %)	25 (89 %)		0.4
Colonization pressure, total days[a]	2.5 [1.7–4]	5.8 [4.3–10]		<0.001
Antibiotic therapy within 1 year	94 (51 %)	16 (57 %)		0.55
Ab <1 year and broad-spectrum	79 (43 %)	16 (57 %)		0.16
Ab <3 mo.	75 (41 %)	14 (50 %)		0.36
Ab <3 mo. and broad-spectrum	63 (35 %)	14 (50 %)		0.12
Ab <3 mo., broad-sp.and >10 days	36 (20 %)	11 (39 %)	2.6 (1.1–6)	0.021
Aminopenicillins	13 (7 %)	1 (4 %)		0.7
Penicillin + iBL	30 (17 %)	10 (36 %)	2.7 (1.1–6.4)	0.02
Fluoroquinolones	11 (6 %)	6 (21 %)	4.2 (1.4–12)	0.015
3GC	21 (12 %)	9 (36 %)	3.6 (1.4–9)	0.01
Imipenem	2 (1 %)	1 (4 %)		0.3
Ab in ICU before acquisition				
Days of therapy	7 [5–11]	8.5 [4.5–19]		0.052
Aminopenicillins	39 (21 %)	7 (25 %)		0.64
Duration	6 [3–9]	6 [3.5–7.5]		
Penicillin + iBL	99 (54 %)	21 (75 %)	2.5 (1–6.3)	0.035
Duration	5 [3–7]	7 [4–9]		
Fluoroquinolones	14 (8 %)	4 (14 %)		0.27
Duration	5 [3.3–12.3]	2.5 [1-4.5]		
3GC	60 (33 %)	11 (39 %)		0.48
Duration	5 [3–7]	6 [4–8]		
Imipenem	26 (14 %)	11 (39 %)	3.9 (1.7–9)	0.003
Duration	2.5 [2–5]	3 [2.5–4.5]		
ICU-acquired infection	44 (24 %)	20 (71 %)	8.0 (3.3–19)	<0.001
Outcomes				
Duration of ICU stay	9 (7–14)	24 (17–34)		<0.001
Mechanical ventilation	91 (50 %)	22 (79 %)	3.7 (1.4–9.7)	0.004
Duration of MV	7.5 [5–14]	19 [10–27]		0.001
Dialysis for acute renal failure	15 (8 %)	6 (21 %)	3.1 (1.1–8.7)	0.04
Alive	154 (84 %)	18 (64 %)	0.35 (0.14–0.8)	0.014

Ab antibiotic, *AKI* acute kidney injury, *broad-sp.* broad-spectrum, *3GC* third generation cephalosporin, *iBL* beta-lactamase inhibitor, *[IQR]* interquartile range (25–75 %); *MV* mechanical ventilation

[a] Colonization pressure is expressed as the sum of the daily proportion of all other patients colonized during the stay of a given patient

incidence of ESBL-PE has markedly increased in Europe during the past decade, including in the community [3, 5, 10, 12, 13]. Of concern, *E.coli* has emerged as the most common microorganism recovered from ESBL-PE carriers at admission; however, *K. pneumonia* and *E. cloacae* remain the most common ICU-acquired ESBL-PE microorganisms.

The increasing prevalence of ESBL-PE carriage on ICU admission raises important questions on empiric therapy policies in patients presenting with infection, which may include the use of a carbapenem as first-line therapy. However, carbapenemase-producing enterobacteriaceae have now emerged (notably among *Klebsiella pneumoniae*) as a group of highly drug-resistant gram-negative bacilli causing infections associated with significant morbidity and mortality [32]. Since the emergence of antibiotic resistance is associated with widespread broad-spectrum antibiotic use, intensivists may now be close to a dead end without the cautious use of carbapenems [21]. In this context, examining the

Table 4 Adjusted odds ratio for ESBL acquisition among 212 patients staying in ICU for 5 days or more

Predictor	Odds ratio	[95 % CI]
Age > 75 years	6.3	[2.17–18.6]
Male gender	3.5	[1.03–11.7]
Colonization pressure[a]	1.3	[1.18–1.49]
3GC within past 3 months	4.8	[1.52–15.0]
B-lactam + inhibitor within past 3 months	3.5	[1.22–10.1]

3GC third generation cephalosporin

[a] Colonization pressure is expressed as mean (daily number of colonized patients/beds occupied) × number of days in ICU prior to ESBL colonization

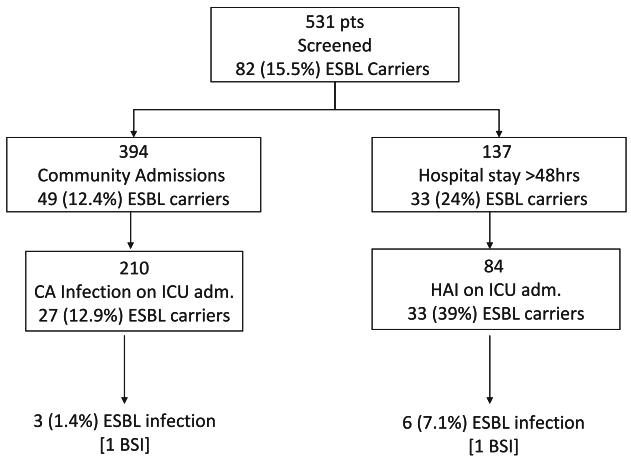

Fig. 1 ESBL colonization and infection on ICU admission. Breakdown of patients by carriage status of extended-spectrum beta-lactamase (ESBL) producing enterobacteriaceae (ESBL-PE) on ICU admission among those admitted from the community ($N = 394$) or having stayed in the hospital for 2 days or more before ICU admission ($N = 137$) and corresponding number of patients having infection on ICU admission (or within 48 h of admission) with an ESBL-PE microorganism, including those having bloodstream infection (BSI). *CA* community-acquired, *HAI* hospital-acquired infection

incidence and risk factors for colonization and infection with such microorganisms might help better targeting empiric therapy. Our results suggest that, despite the high colonization rate at ICU admission, infections caused by ESBL-PE remain very infrequent (only 3 % of infected patients in our study). Thus, limited use of empiric treatment with carbapenems targeting ESBL-PE can still be recommended, even in a setting with a high endemic rate of ESBL-PE carriage. Restricting their use to selected patients having risk factors for colonization with ESBL-producing bacteria at ICU admission is likely to limit unnecessary exposure to carbapenems in the ICU.

Previous studies have shown that patients infected with ESBL-producing bacteria have identifiable clinical characteristics that can be used readily upon ICU admission [28, 29, 31, 33, 34], such as male gender, being elderly and/or a nursing home resident, recent hospitalization, or exposure to any antibiotic [10]. We identified prior hospital admission in another country, transfer from another ICU, surgery within the past year, and prior neurologic disease as independent risk factors for colonization with ESBL-PE at ICU admission. Predictive factors in the subgroup of patients admitted from the community included a previous hospital admission within 3–12 months before ICU admission and a history of urinary tract disease. Interestingly, our study confirms that exposure to third generation cephalosporin within months before ICU admission was an independent risk factor for colonization with ESBL-PE at ICU admission, irrespective of the patient's location before ICU admission.

Despite the high colonization pressure with ESBL-PE, the rate of ICU-acquired colonization with these microorganisms was relatively low, at 6 % overall and 9 % in the population staying in the ICU for >3 days. This is probably explained mostly by the high hand hygiene compliance rate (>80 %) of personnel in our unit during the study period resulting from the ongoing hand hygiene improvement program and possibly from the routine use of daily chlorhexidine body washings. Among the 212 patients staying in the ICU for >5 days and non-colonized on admission, only 28 (13 %) acquired ESBL-PE carriage, mostly with *E. cloacae* ($n = 13$, 46 %) and *K. pneumoniae* ($n = 10$, 36 %), but rarely with *E. coli*. Acquisition of ESBL-PE during the ICU stay was associated with age >75 years, male gender, colonization pressure, and administration of a third generation cephalosporin or a β-lactam/inhibitor combination within 3 months before ICU admission. Intriguingly, exposure to various antibiotic classes during the ICU stay did not remain associated with ESBL-PE acquisition after multivariable analysis. However, colonization pressure remained associated with acquisitions, and a substantial proportion of these were due to *K. pneumoniae* and *Enterobacter* spp, for which horizontal transmission may predominate over selection of resistance [35].

Important features of our study include its prospective design, accounting for antibiotic exposure before and during the ICU stay, in the unique setting of a sustained controlled high hand hygiene compliance rate and absence of additional contact precautions, which helps interpreting the results. First, despite the high level of standard precautions, ESBLE-PE acquisitions still remained substantial and related to colonization pressure. Standard precautions alone thus do not appear sufficient to control the spread of ESBL-PE within ICUs. Second, the use of third generation cephalosporins should be limited, as prior exposure to these drugs was a risk factor both for carriage on admission and for acquisition. Third, a different control policy may be justified against *E.coli* on one hand and *K. pneumoniae* and *Enterobacter* spp. on the other. While there are no universal guidelines concerning infection

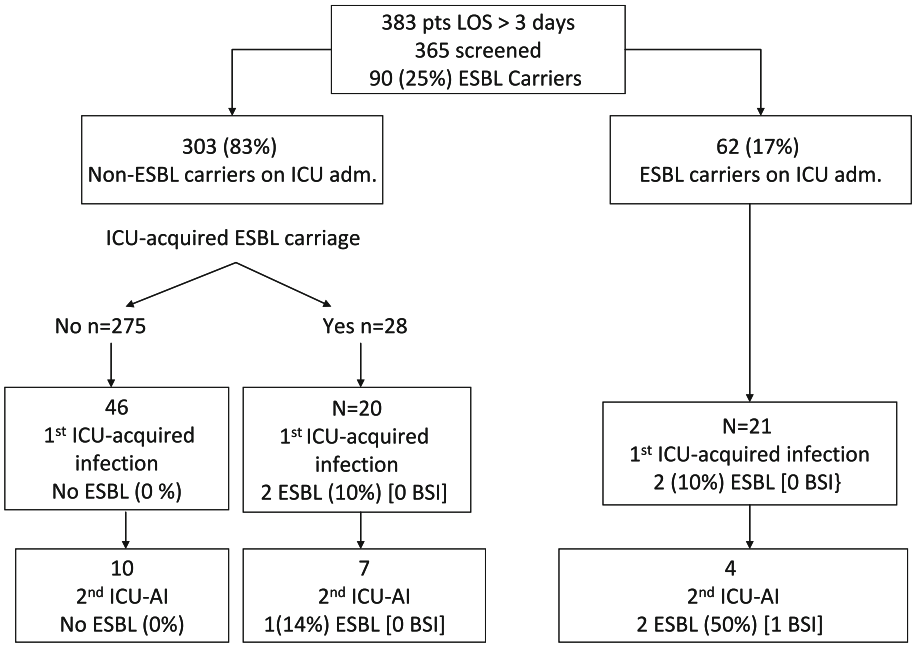

Fig. 2 ICU-acquired ESBL colonization and infection. Number (%) of patients with first and secondary infections caused by ESBL-PE among those acquiring infection during the ICU stay contrasting carriers and non-carriers and patients colonized on admission or acquiring ESBL-PE carriage. *AI* acquired infection, *BSI* bloodstream infection

control measures for ESBL-PE carriers, our data suggest that additional measures may be warranted to control the spread of the latter species. Indeed, *K. pneumoniae and Enterobacter* are frequently involved in hospital outbreaks; in addition, environmental contamination is more frequent with ESBL-producing *Klebsiella* than with *E coli* [36]. Therefore, intensifying control measures might prove useful for these two species.

Overall, there were 294 infections at admission and 108 ICU-acquired infections, of which 3 and 6.5 % were caused by ESBL-PE, respectively. Infections caused by ESBL-PE were thus relatively infrequent in our study despite the high carriage rate. In a prospective study of 455 consecutive episodes of *K. pneumoniae* bacteremia in 12 hospitals from seven countries conducted in 1996–1997, 85 (19 %) were due to an ESBL-producing strain [37]. This rate was higher among the 253 nosocomial infections (31 %), particularly those acquired in the intensive care unit (43 %). In our patients, ESBL-PE caused 3 % of all ICU-acquired bacteremias and 5 % of ICU-acquired bloodstream infections caused by gram-negative bacilli. Although ventilator-associated pneumonia (VAP) is the main source of ICU-acquired infections [40], only one of our patients developed a VAP caused by an ESBL-PE.

A major risk factor for nosocomial infection is prior colonization [22]. All but one of the patients who had an ICU-acquired infection caused by ESBL-PE were found to have been previously colonized a median of 5 days [3–9] before infection. ESBL-PE caused only 4.6 % of 87 first episodes but 14 % of 21 secondary episodes of ICU-acquired infection. Among the 90 ESBL-PE carriers staying in the ICU for more than 3 days, these organisms caused 10 % of the first episodes and 27 % of the second episodes of ICU-acquired infections. In previous studies, performed in the context of much lower prevalence rates on ICU admissions, 9–25 % of ESBL-colonized patients acquired ESBL-PE infection [28, 31]. In our environment, carbapenems can thus be viewed as drugs of choice for empiric therapy of late ICU-acquired infections, especially in known carriers, thus providing coverage for ESBL-PE, as well as for drug-resistant *Pseudomonas aeruginosa*, another major cause of late ICU-acquired infection. Indeed, 73 patients received carbapenems during the 8-month period, mostly for empiric therapy of ICU-acquired infections.

Our study has some limitations. Because the study was monocentric, the results cannot be extrapolated to other ICUs with different epidemiologies and infection control policies and standards, especially regarding the acquisition of ESBL-EB. Colonization relied on rectal swabbing, which does not provide 100 % sensitivity for the detection of ESBL carriage, thus possibly resulting in misclassification of patients. Confronting epidemiological information with the results of molecular typing of isolates could have provided a better insight into the risk of cross-transmission between different species. A final limitation of our study is the relatively small number of infections, thus limiting our ability to identify specific risk factors for infection. In addition, despite careful examination of patients' records, it is likely that we did not retrieve all antimicrobial drugs that patients may have received as outpatients before their hospital admission. However, the information collected in our study reflects the information available to the intensivist in real-life practice when confronted with decisions on antibiotic therapy in patients presenting with sepsis in the ICU.

To conclude, since improving carbapenem use is currently a major challenge for intensivists, our analyses of risk factors for colonization on admission and acquisitions of ESBL-PE may be useful for identifying which patients may warrant empiric therapy targeting these organisms in the context of high endemic rates, even on ICU admission. They may also contribute to future antibiotic stewardship programs and/or interventional studies to help control ESBL-PE [38, 39]. Larger scale studies are needed to identify risk factors for ICU-acquired ESBL infection and to assess patterns of use of empiric therapy with carbapenems according to the knowledge of ESBL colonization status of the patient.

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Conflicts of interest All authors report no conflict of interest relevant to this study.

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